Exploring the Reactivity of a Malononitrile Derivative with a Nitroalkene

An Honors Thesis (HONR 499)

by

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Abstract

Michael addition of malononitrile as nucleophiles to nitroalkenes as electrophiles has been scarcely explored in organic chemistry. These two groups are widely known for their importance in pharmaceuticals, as well as medical and bioactivity usages. Malononitriles have been used as an intermediate to the formation of cancer treatments; nitroalkenes have been a building block for therapeutic drugs treating reflux esophagitis. Synthesizing these two molecules with a carbon-carbon bond would expand organic chemistry knowledge as well as create possibilities for advances in the medicinal world. Using 4-methoxybenzylmalononitrile and 4-chloro-β-nitrostyrene as reactants, I was able to synthesize 2-[1-(4-chlorophenyl)-2-nitroethyl]-2-(4-methoxybenzyl)malononitrile while testing multiple reaction catalysts in the process. Several catalysts with varying equivalents produced different amounts of the product.

Acknowledgements

I would like to thank Dr. Robert Sammelson for advising me through this project. Without his guidance, encouragement and positive attitude, I would not have been able to complete this difficult task.

I would like to thank the Chemistry Department for providing the necessary materials and equipment needed to complete the research.

Much-needed thanks to Haifa for her collaboration with procedures and results as we conducted similar research.

I would like to thank the Butler Undergraduate Research Conference for allowing me the opportunity to present my research and share with my peers.

Lastly, I would like to thank Merinda, Bianca, and my parents, Jeff and Nicole, for their endless encouragement and allowing me the opportunity to feel like a genius when they ask me to explain the topic of my thesis.

Author's Statement

Importance of the Research

The research presented is a contribution to the growth of organic chemistry. Reacting malononitriles with nitroalkenes is an area of discipline that has been scarcely explored, therefore I am hopeful that my research shines some light on the topic so as to further develop the chemistry. More so, malononitriles and nitroalkenes are known as reagents in the synthesis of pharmaceuticals, and for medicinal and bioactivity usage. Malononitrile is an important building block for the syntheses of pharmaceuticals such as vitamin B1, adenine, known as vitamin B4, and triamterene, which can treat retention and high blood pressure. More importantly, malononitrile has been used as an intermediate for methotrexate, a treatment for cancer of the blood, bone, lung, breast, head, and neck, and also treatment for rheumatoid arthritis and psoriasis. Nitroalkenes have been used as building blocks for producing therapeutic drugs treating reflux esophagitis, an antispasmodic such as baclofen. Thus, reacting malononitrile molecules with nitroalkenes results in a product that could contain medicinal treatments not yet discovered.

Besides its importance to science, this project gave me the research experience that has been lacking in my education. I learned how to use several databases to search for articles and procedures that provided insight into my topic. These databases included SciFinder Scholar, ACS Publications, and Web of Science. Once I located a procedure that appeared to be similar to the chemistry I was going to preform, I was able to adjust the procedure according to what I needed. For example, if I needed 0.5 millimoles (mmol) of a reactant but the procedure called for 10 mmol, I was able to preform the required calculations to correct for the smaller amount of reactant needed. Additionally, some procedures were used as templates in which I changed the

amount of time required for the reaction or the way starting material was added to the reaction flask. I was able to adjust procedures accordingly to fit my research.

After prepping the reactions, I had to physically conduct the experiments and analyze results. I was able to learn how to use new equipment, such as a Rotavapor to evaporate the solvent and ^{1}H NMR to determine if the expected product was effectively synthesized. In doing so, it was the first time I was able to conduct experiments outside of a structured teaching laboratory. This is a vital component to my educational experience as I not only gained more knowledge regarding techniques and equipment, but gained confidence in my laboratory skills as a chemist.

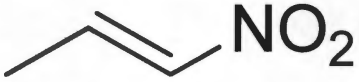
With this confidence boost, I have decided that pursuing a laboratory setting conducting research is a possible career path. Before this experience, I was clueless as to what I would be pursuing after graduation. Graduate school and medical school seemed like possibilities, but neither truly spoke to me as immediate desirables. Upon making this decision, the type of career setting and type of chemistry I wanted to pursue was unknown to me. Therefore, I elected to approach the laboratory work force to not only start my career, but also gain more knowledge and experience to determine my life-long career goal. Through this research I found that I enjoy working in a laboratory setting and now have an idea of what my future may entail.

Research and Results

The main idea of my thesis is identifying a catalyst that would help aid the reaction between a malononitrile and a nitroalkene to form a carbon-carbon bond between the two molecules and create one compound. A catalyst is a substance that is not consumed by the reaction, but rather assists the reaction by lowering the amount of energy it takes to transition from reactants to products.

Malononitrile has a molecular formula of $CH_2(CN)_2$. This means that two cyanide (CN) compounds are single bonded to one central carbon with two hydrogens attached. A cyanide compound consists of a carbon triple bonded to nitrogen. The following picture gives an idea of what a malononitrile compound looks like:

Nitroalkene is a series of unsaturated open-chain hydrocarbons (CH) with a nitrogen dioxide (NO_2) attached. The unsaturated identification refers to the chain of carbons containing at least one double bond, rather than all single bonds. An open chain means there are no rings or enclosed assemblies within the structure. These compounds are sometimes said to be in the ethylene or olefin series, which means nitroalkene can often be referred to as nitrostyrene or nitroolefin. These terms are interchange able within my thesis. The following picture gives an idea of what a nitroalkene compound may look like:



These compounds, malononitriles and nitroalkenes, can be bonded to other structures such as aromatic rings, which is a hexagonal ring of six carbons with alternating double bonds. In this research, both compounds are bonded to aromatic rings.

The type of reaction that occurs between the malononitrile and the nitroalkene is called a Michael addition. This addition is commonly used for the formation of carbon-carbon bonds. It is the nucleophilic addition of a carbanion (Michael donor) or another nucleophile to an unsaturated compound (Michael acceptor) or electrophile. In this research, the malononitrile is the nucleophile, donating an electron pair to be used in the formation of the chemical bond. The nitroalkene is the unsaturated, electrophilic compound that accepts the free electron pair during

the reaction. The donation and acceptance of electron pairs between the two molecules is what creates the carbon-carbon bond for the synthesis of one compound.

The first catalyst I tested in the reaction was potassium carbonate (K_2CO_3), due to the article procedure I chose to follow. The article used K_2CO_3 and another compound as the catalyst, therefore I decided to single out the K_2CO_3 as an initial attempt. I used one equivalent of the catalyst with one equivalent each of the reactants. In other words, for every one malononitrile compound and one nitroalkene compound, there was one potassium carbonate present in the reaction. After completion and analysis of the product, the amount of catalyst was adjusted; catalysts usually do not need to be utilized in large amounts. Therefore, potassium carbonate was adjusted to 0.1 equivalent, 0.02 equivalent, and 0.005 equivalent, a reduction of 10, 5, and 4, respectively. Research is often a trial-and-error experiment; trying one thing, adjusting and trying it again to evaluate results. This is the approach I took when deciding what equivalents to use for the catalysts.

Next I used sodium carbonate (Na_2CO_3) in 0.1 equivalents and 0.02 equivalents. Sodium carbonate was chosen because it reacts similarly to potassium carbonate but still possess different chemistry because of the sodium molecules. I did not attempt a 1 equivalent reaction due to the inefficiency the large amount resulted in with the first catalyst. A 0.05 equivalent was not chosen either because the grams required were too small to weigh on a scale.

The third catalyst attempted was sodium bicarbonate ($NaHCO_3$) in 0.1 equivalents and 0.02 equivalents. This substance possesses similar chemistry to potassium carbonate and sodium carbonate, however since it is a salt it reacts differently. I did not attempt a 1 equivalent or 0.05 equivalent for the same reasons stated above.

As a result, the product was successfully synthesized with the majority of the catalysts. After further testing, it was concluded that the product was synthesized with 0.1, 0.02, and 0.005 equivalents of K_2CO_3, 0.1 and 0.02 equivalents of $NaHCO_3$, 0.1 and 0.02 equivalents of Na_2CO_3, but was not synthesized with 1 equivalent of K_2CO_3. The anticipated outcome of this research was formation of the product, but how that was going to happen was an uncertain process.

Furthermore, there was another result that was unexpected; malononitrile, a reactant, was still present upon determining if the product was synthesized. It appears that the nitroalkene disappears before completely reacting with the malononitrile, therefore leaving the malononitrile still existent in the finished product. More testing needs to be determined to identify if there is a side reaction occurring that causes the nitroalkene to vanish before reacting with the malononitrile.

Reflect and Future

At this point, I wish I had more time to conduct more research. When starting my thesis, I made a list of catalysts and other conditions I wanted to attempt. Although I knew I wasn't going to get through all of what I listed, I wanted to get as much done as I could in hopes of making significant progress for the next undergraduate that continues the research. Chemistry is an ever changing, ever growing discipline. There is much more exploration that needs to be conducted within this area, yet knowing I have made a contribution is gratifying.

I am hoping the next student that takes over the research will pick up where I left off, continuing the list of recommended catalysts and conditions. Those catalysts I hope are attempted in the future are sodium acetate (NaOAc), ammonium acetate (NH_4OAc), 18-crown-6 in combination with K_2CO_3, and 12-crown-4 in combination with Na_2CO_3. Conditions I hope are tested include temperature change, adjusting the pH, using organic or inorganic compounds, and

exploring the effect of different aromatic substituents. A change in the reaction's environment is a huge factor that can lead to a reaction proceeding differently. Additionally, I hope the next student will be able to look into exactly what is causing the malononitrile to remain present after completion of the reaction, whether there is in fact a side reaction or if it is a different problem. Adjusting the equivalence in the reaction to entirely produce the desired product is starting point. It may be that the nitroalkene is needed in excess to ensure all of the malononitrile reacts; increasing the mmol amount of nitroalkene to twice as much as malononitrile is where I would start. Provided all the malononitrile reacts with this increase and nitroalkene is still present, further adjustment the equivalents will be required until no reactants remain after the reaction. This something I am still curious about and wished I could have solved.

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Introduction

Michael addition of electron-deficient nitroolefins is an important reaction in organic synthesis, which provides access to useful functionalized nitroalkenes [1]. Recently, the development of organo-catalytic asymmetric Michael addition reactions of nitroalkenes has received growing attention. Carbon-carbon bond forming reactions [1] are often a difficult task for organic chemists. These reactions utilize simpler building blocks to produce complex products [2].

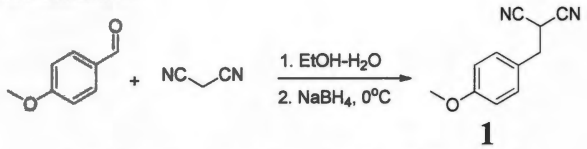
While many researchers have developed addition methods of aldehydes, ketones, malonate and other organic compounds to nitroolefins, Michael addition reactions of malononitrile to nitroolefins have been hardly explored [1].

Preparation of Malononitrile

Malononitrile is a commonly known and widely used reagent in the synthesis of pharmaceuticals, pesticides, and organic semiconductors. The unique reactivity of this compound promotes extensive applications in organic chemistry, even more so than other known CH-acids [3]; the nitrile group is a versatile functional group available for many further transformations [4]. Malononitrile and its derivatives have been vastly used to synthesis products with aldehydes, ketones, heterocyclic compounds, and several other reagents [3].

The malononitrile derivative synthesized for this research was derived from a one-pot reductive alkylation with an aromatic aldehyde [2], scheme 1.

Scheme 1



1

Synthesis of 4-methoxybenzylmalononitirle

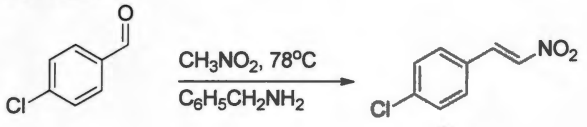
The malononitrile derivative, 4-methoxy-benzylmalononitrile **1**, was chosen as the primary derivative due to the high percent yield and low reaction time reported in Tayyari's [2] procedure. Compound **1** was produced with decent yield, 67%.

Preparation of Nitroalkene

The ready conversion of the nitro group into a variety of diverse functionalities allows the nitroalkene to be a versatile synthetic block for bioactivities and medicinal usage [5]. For example, nitroalkenes have been found to be useful tool for producing therapeutic drugs treating reflux esophagitis, an antispasmodic such as baclofen [6]. Nitroalkene is also a chemical precursor for slimicides and dyes [7].

The nitroalkene derivative synthesized for this research was derived from a Henry condensation [5,6], scheme 2.

Scheme 2



2

Synthesis of 4-chloro-β-nitrostyrene

The nitroalkene derivative, 4-chloro-β-nitrostyrene **2**, was chosen as the primary derivative due to the high preference of 4-chlorobenzaldehyde as the benzaldehyde derivative in the Takeda [6] Henry

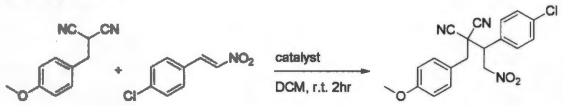
condensation procedure. Compound **2** was produced in a 28% yield.

Michael Addition Reaction

To date, there have been very few studies using nitroolefins as Michael reaction acceptors [1,4]. Further, malononitriles have been relatively less explored as Michael addition nucleophiles due to the high reactivity and incapability of two-point binding with the catalyst [4].

This research makes an attempt to form a carbon-carbon bond at the α position of the malononitrile, utilizing compound **1** as the nucleophile and compound **2** as the electrophile, along with several different catalysts. The synthesis of formation procedure for 2-[1-(4-chloro-phenyl)-2-nitroethyl]-2-(4-methoxybenzyl)malono-nitrile **3** was derived from Xue's [8] general procedure for alkylation reaction, scheme 3.

Scheme 3



3

Synthesis of 2-[1-(4-chlorophenyl)-2-nitroethyl]-2-(4-methoxybenzyl)malononitrile

Catalyst	Results (Product : Reactant*)
100% K_2CO_3	Poor Yield 0.14:1
10% K_2CO_3	Good Yield 1.5:1
2% K_2CO_3	Average Yield 1.2:1
0.5% K_2CO_3	Good Yield 2.1:1
10% Na_2CO_3	Average Yield 1.1:1
2% Na_2CO_3	Good Yield 1.8:1
10% $NaHCO_3$	Average Yield 1.2:1
2% $NaHCO_3$	Good Yield 1.5:1

Table 1. Reactions preformed at 0.5 mmol scales. 2% Na_2CO_3, 10% and 2% $NaHCO_3$ reactions preformed at 0.1 mmol scales. Results determined by ^1H NMR analysis and integration. * Reactant present is 4-methoxybenzylmalononitrile.

As shown in Table 1, a full equivalent of K_2CO_3 as a catalyst yields the worst results in terms of product formation, with a 0.14:1 ratio of product to reactant. This was somewhat expected since large amounts of catalysts are usually unnecessary in a reaction, however it further shaped the research development as full equivalents were no longer tested. 2% K_2CO_3, 10% Na_2CO_3, and 10% $NaHCO_3$ produced average yields, equivalent to 1.1-1.2:1 ratio. This concludes that the catalyst equivalents were too small to fully aid the reaction completion. 10% of K_2CO_3, 2% Na_2CO_3 and 2% $NaHCO_3$ produced the good yields, a 1.5-1.8:1 ratio. These ratios appear to be on the right track as more product was being produced than there was reactant left behind. 0.5% K_2CO_3 produced the best results with a 2.1:1 ratio. This indicates that smaller amounts catalyst may produce the best results. However, these catalysts did not complete the reaction.

After analysis of the ^1H NMR spectra, compound **1** emerges as the remaining reactant within the product. Further research needs to be conducted to determine why the malononitrile is still present.

Conclusion

Reactants **1** and **2** were prepared in excess to attempt a Michael reaction carbon-carbon bond formation at the α position of the malononitrile utilizing several catalysts. It was found that 0.5% K_2CO_3, 10% K_2CO_3, 2% Na_2CO_3, and 2% $NaHCO_3$ produced the highest ratio in terms of product formation to reactant remaining. The catalysts appear to produce the predicted product, but do not complete the reaction.

It appears that the smaller amounts of catalyst produce the best results in terms of product formation. However, it would be ideal that each equivalent be tested again to ensure the ratios are accurate with product synthesis.

While synthesis of compound **3** occurred as anticipated, there were other unexpected results. Compound **1** was still present at the completion of the reaction. A question rises as to whether or not there is a side reaction occurring that depletes compound **2** before completely reacting with the malononitrile derivative.

Experimental Section

4-Methoxybenzylmalononitrile (1). Malononitrile (0.3699 g, 5.25 mmol) was added to a solution of anisaldehyde (0.6884 g, 5 mmol) in ethanol (4 mL), with additional ethanol (4 mL) added as well. Solution was allowed to stir for 10 min at room temperature, washing with ethanol when needed. Filtrate for 30 min, washing with chilled ethanol and DI water. Filtrate and wash the filtrate. The intermediate was combined with ethanol (8 mL) and placed in a 0 °C ice bath for 30 min. Sodium borohydride (0.1000 g, 2.5 mmol) was added to the reaction mixture and vigorously stirred for 20 min. In a 50 mL beaker, DI water (25 mL) and the reaction mixture were com-bined, placed in the ice bath and stirred. 2M hydrochloric acid was added till the hydride was quenched. Vacuum filtration was conducted, washing with cold DI water. White solid (0.6204 g, 67%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, J=8.8 Hz, 2H), 6.91 (d, J=8.8 Hz, 2H), 3.85 (t, J=7.0 Hz, 1H), 3.81 (s, 3H), 3.23 (d, J=7.0 Hz, 2H). NMR spectra shown in Appendix A.

4-Chloro-β-nitrostyrene (2). A solution of 4-chlorobenzaldehyde (2.0125 g, 13.5 mmol) and benzylamine (1.6001 g, 14.3 mmol) in acetic acid (10.2 mL) was heated and maintained between 75 °C–83 °C. Nitromethane (3.2609 g, 53.4 mmol) was dripped into the solution in 10 min intervals for 80 min, after which the solution continued stirring for an additional 40 min. Reaction mixture cooled to 50 °C and DI water (10.2 mL) was dripped in over a 80 min period. Cooled to 6 °C–10 °C and maintained for 50 min. Filtered and washed with DI water (10 mL). Crystals were dissolved in toluene (6.6 mL) at 50 °C and subjected to liquid separation, washed with DI water (3 mL). Product was crystalized in an ice bath and dried over night. Yellow solid (0.6200 g, 28%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, J=13.5 Hz, 1H), 7.55 (d, J=13.5 Hz, 1H), 7.49 (d, J=8.7 Hz, 2H), 7.43 (d, J=8.7 Hz, 2H). NMR spectra shown in Appendix B.

General Procedure for Compound 1 and Compound 2. 4-methoxybenzylmalononitrile (0.5 mmol) and catalyst were dissolved in DCM (0.5 mL). 4-chloro-β-nitrostyrene (0.5 mmol) was added to the flask and stirred for 120 min at room temperature. Solution dissolved in DCM (1.0 mL) and DI water (0.5 mL), and subjected to liquid separation. Mixture was placed on a Rotavapor at 60 °C for 30 min to evaporate excess DCM. NMR spectra shown in Appendix C-J.

2-[1-(4-Chlorophenyl)-2-nitroethyl]-2-(4-methoxybenzyl)malononitrile; 100% K_2CO_3. 4-methoxybenzylmalononitrile (0.0940 g, 0.5 mmol) and potassium carbonate (0.0774 g, 0.5 mmol) were dissolved in DCM (0.5 mL). 4-chloro-β-nitrostyrene (0.0983 g, 0.5 mmol) was added to the flask and stirred for 120 min at room temperature. Solution dissolved in DCM (1.0 mL) and DI water (0.5 mL), and subjected to liquid separation. Mixture was placed on a Rotavapor at 60 °C for 30 min to evaporate excess DCM. Dark orange solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.23 (d, J=6.6 Hz, 2H) [malononitrile], 3.10 (d, J=13.2 Hz, 1H), 2.98 (d, J=13.5 Hz, 1H). NMR spectra shown in Appendix C.

2-[1-(4-Chlorophenyl)-2-nitroethyl]-2-(4-methoxybenzyl)malononitrile:
10% K_2CO_3. Procedure analogous to the one stated above was conducted. 4-methoxybenzylmalononitrile (0.0953 g, 5 mmol), potassium carbonate (0.0077 g, 0.05 mmol), 4-chloro-β-nitrostyrene (0.0988 g, 0.5 mmol). Light yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (dd, J=32.2 Hz, 6.2 Hz, 2H), 7.23 (t, J=21.8 Hz, 2H), 6.91 (m, J=13.1 Hz, 4H), 5.09 (m, J=41.4 Hz, 2H), 4.07 (dd, J=15.4 Hz, 5.1 Hz, 1H), 3.23 (d, J=6.96 Hz, 2H) [malononitrile], 3.03 (d, J=13.9 Hz, 1H), 2.83 (d, J=13.9 Hz, 1H). NMR spectra shown in Appendix D.

2-[1-(4-Chlorophenyl)-2-nitroethyl]-2-(4-methoxybenzyl)malononitrile:
2% K_2CO_3. Procedure analogous to the one stated above was conducted. 4-methoxybenzylmalononitrile (0.0936 g, 0.5 mmol), potassium carbonate (0.0018 g, 0.01 mmol), 4-chloro-β-nitrostyrene (0.0975 g, 0.5 mmol). Light yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (dd, J=28.8 Hz, 9.8 Hz, 2H), 7.23 (t, J=17.8 Hz, 2H), 6.91 (m, J= 13.1 Hz, 4H), 5.09 (m, J=32.7 Hz, 2H), 4.06 (dd, J=13.7 Hz, 4.95 Hz 1H), 3.23 (d, J=6.3 Hz, 2H) [malononitrile], 3.04 (d, J=16.5 Hz, 1H), 2.83 (d, J=12.4 Hz, 1H). NMR spectra shown in Appendix E.

2-[1-(4-Chlorophenyl)-2-nitroethyl]-2-(4-methoxybenzyl)malononitrile:
0.5% K_2CO_3. Procedure analogous to the one stated above was conducted 4-methoxybenzylmalononitrile (0.0937 g, 0.5 mmol), potassium carbonate (0.0002 g, 0.0025 mmol), 4-chloro-β-nitrostyrene (0.0978 g, 0.5 mmol). Light yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (dd, J=21.8 Hz, 12.9 Hz, 2H), 7.23 (t, J=15.0 Hz, 2H), 6.91 (m, J=16.2 Hz, 4H), 5.09 (m, J=32.9 Hz, 2H), 4.07 (dd, J=15.9 Hz, 5.8 Hz, 1H), 3.23 (d, J=10.2 Hz, 2H) [malononitrile], 3.04 (d, J=14.6 Hz, 1H), 2.83 (d, J=15.9 Hz, 1H). NMR spectra shown in Appendix G.

2-[1-(4-Chlorophenyl)-2-nitroethyl]-2-(4-methoxybenzyl)malononitrile:
10% Na_2CO_3. Procedure analogous to the one stated above was conducted 4-methoxybenzylmalononitrile (0.0943 g, 0.5 mmol), sodium carbonate (0.0050 g, 0.05 mmol), 4-chloro-β-nitrostyrene (0.0978 g, 0.5 mmol). Light yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (dd, J= 27.21 Hz, 9.06 Hz, 2H), 7.22 (t, J=22.1 Hz, 2H), 6.91 (m, J=15.6 Hz, 4H), 5.12 (m, J=37.9 Hz, 2H), 4.07 (dd, J=13.7 Hz, 4.95 Hz, 1H), 3.23 (d, J=4.7 Hz, 2H) [malononitrile], 3.0 3(d, J=14.3 Hz, 1H), 2.84 (d, J=15.6 Hz, 1H). NMR spectra shown in Appendix F.

2-[1-(4-Chlorophenyl)-2-nitroethyl]-2-(4-methoxybenzyl)malononitrile:
2% Na_2CO_3. Procedure analogous to the one stated above was conducted 4-methoxybenzylmalononitrile (0.0191 g, 0.1 mmol), sodium carbonate (0.0006 g, 0.002 mmol), 4-chloro-β-nitrostyrene (0.0205 g, 0.1 mmol). Light yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (dd, J=32.0 Hz, 11.0 Hz, 2H), 7.24 (t, J=23.4 Hz, 2H), 6.91 (m, J=17.9 Hz, 4H), 5.10 (m, J=41.76 Hz, 2H), 4.07 (dd, J=15.7 Hz, 5.30 Hz, 1H), 3.23 (d, J=8.0 Hz, 2H) [malononitrile], 3.03 (d, J=11.7, 1H), 2.84 (d, J=12.8 Hz, 1H). NMR spectra shown in Appendix J.

2-[1-(4-Chlorophenyl)-2-nitroethyl]-2-(4-methoxybenzyl)malononitrile:
10%$NaHCO_3$. Procedure analogous to the one stated above was conducted 4-methoxybenzylmalononitrile (0.0190 g, 0.1 mmol), sodium bicarbonate (0.0013 g, 0.01 mmol), 4-chloro-β-nitrostyrene (0.0187 g, 0.1 mmol). Light yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (dd, J= 27.48 Hz, 11.5 Hz, 2H), 7.23 (t, J=16.7 Hz, 2H), 6.91 (m, J=16.2 Hz, 4H), 5.09 (m, J=32.4 Hz, 2H), 4.07 (dd, J=15.7 Hz, 5.5 Hz, 1H), 3.24 (d, J=7.9 Hz, 2H) [malononitrile], 3.03 (d, J=12.6 Hz, 1H), 2.84 (d, J=13.4 Hz, 1H). NMR spectra shown in Appendix H.

2-[1-(4-Chlorophenyl)-2-nitroethyl]-2-(4-methoxybenzyl)malononitrile:

2%$NaHCO_3$. Procedure analogous to the one stated above was conducted 4-methoxybenzylmalononitrile (0.0200 g, 0.1 mmol), sodium bicarbonate (0.0001 g, 0.002 mmol), 4-chloro-β-nitrostyrene (0.0213 g, 0.1 mmol). Light yellow solid; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (dd, J=26.8 Hz, 8.56 Hz, 2H), 7.23 (t, J=26.4 Hz, 2H), 6.91 (m, J=14.1 Hz, 4H), 5.10 (m, J=39.9 Hz, 2H), 4.07 (dd, J=15.8 Hz, 5.5 Hz 1H), 3.22 (d, J=11.4 Hz, 2H) [malononitrile], 3.03 (d, J=8.4 Hz, 1H), 2.84 (d, J=14.3 Hz, 1H). NMR spectra shown in Appendix I.

References

[1] Guo, H.M.; Li, J.G.; Qu, G.R.; Zhang, X.M.; Yuan, W.C. *Chirality.* **2011**, *23*, 514-518.

[2] Tayyari, F.; Wood, D.E.; Fanwick, P.E.; Sammelson, R.E. *Synthesis* **2008**, 279-285.

[3] Hassan, E.A.; Elmaghraby, A.M. *ISSR Journals.* **2015**, *16*, 11-46.

[4] Chen, S.; Lou, Q.; Ding, Y.; Zhang, S.; Hu, W.; Zhao, J. *Adv. Synth. Catal.* **2015**, *357*, 2437-2441.

[5] Ying, A.; Xu, S.; Liu, S.; Ni, Y.; Yang, J.; Wu, C. *Ind. Eng. Chem. Res.* **2014**, *53*, 547-552.

[6] Takeda, M.; Kadono, H.; Murakami, K. Method for Producing β-Nitrostyrene Compound. U.S. Patent 8,067,647 B2, November 29, 2011.

[7] Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*(1), 119-125.

[8] Xue, D.; Chen, Y.; Wang, Q.; Cun, L.; Zhu, J.; Deng, J. *Org. Lett.* **2005**, *7*, 5293-5296.

Appendix

A. ^1H NMR 4-methoxybenzylmalononitrile

B. ^1H NMR 4-chloro-β-nitrostyrene

C. ^1H NMR 2-[1-(4-chlorophenyl)-2-nitro-ethyl]-2-(4-methoxybenzyl)malononitrile; 100% K_2CO_3

D. ^1H NMR 2-[1-(4-chlorophenyl)-2-nitro-ethyl]-2-(4-methoxybenzyl)malononitrile; 10% K_2CO_3

E. ^1H NMR 2-[1-(4-chlorophenyl)-2-nitro-ethyl]-2-(4-methoxybenzyl)malononitrile; 2% K_2CO_3

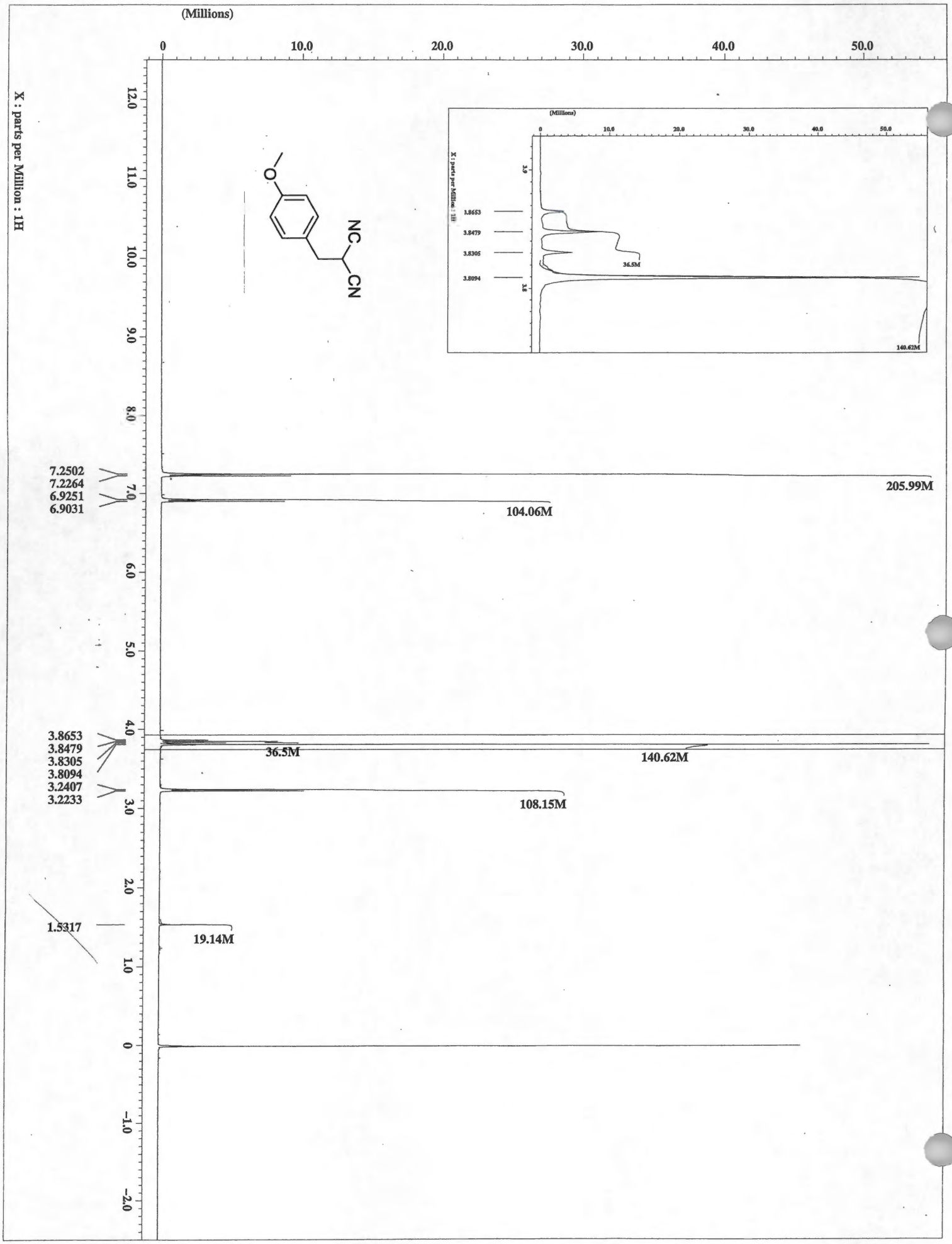
F. ^1H NMR 2-[1-(4-chlorophenyl)-2-nitro-ethyl]-2-(4-methoxybenzyl)malononitrile; 10% Na_2CO_3

G. ^1H NMR 2-[1-(4-chlorophenyl)-2-nitro-ethyl]-2-(4-methoxybenzyl)malononitrile; 0.5% K_2CO_3

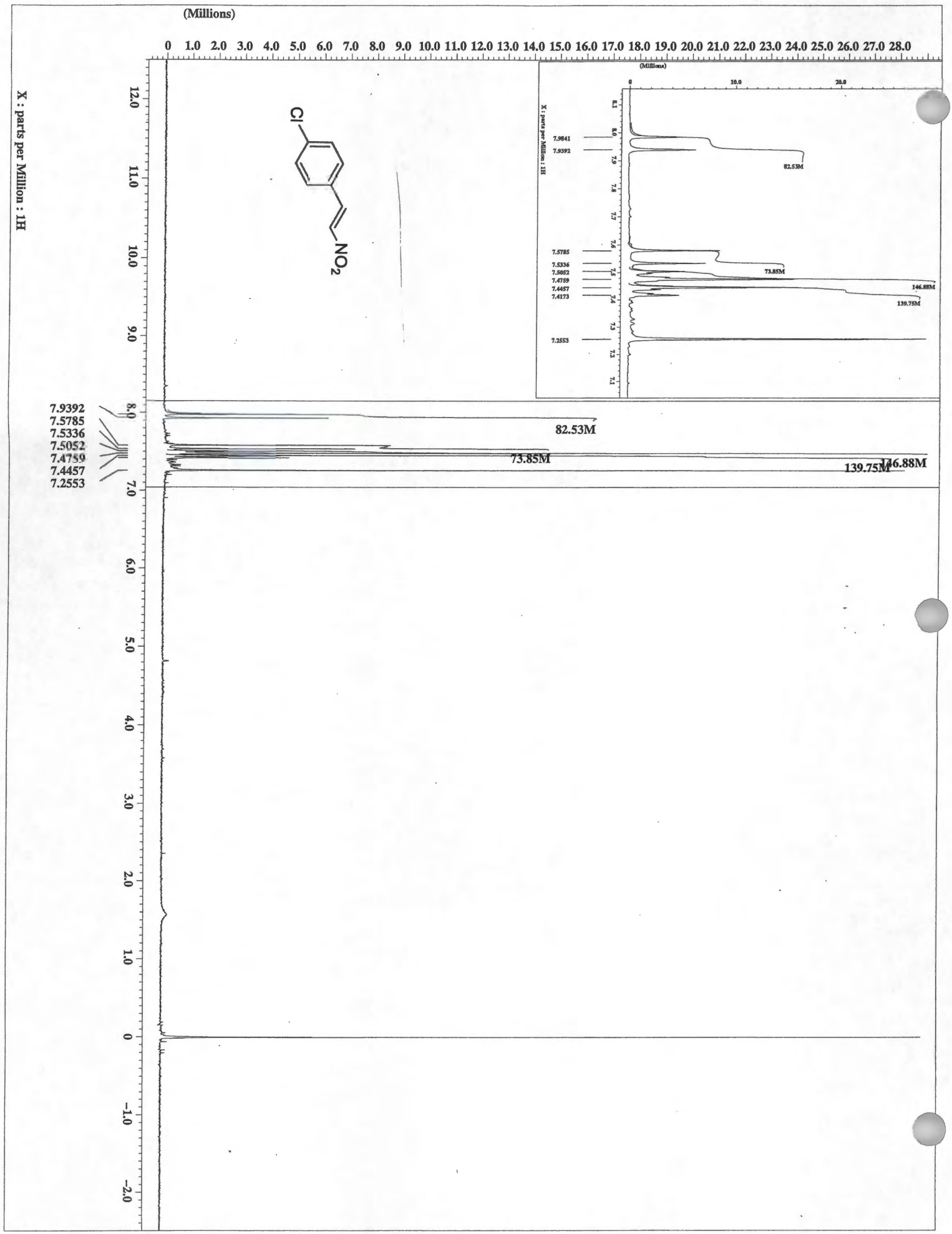
H. ^1H NMR 2-[1-(4-chlorophenyl)-2-nitro-ethyl]-2-(4-methoxybenzyl)malononitrile; 10% $NaHCO_3$

I. ^1H NMR 2-[1-(4-chlorophenyl)-2-nitro-ethyl]-2-(4-methoxybenzyl)malononitrile; 2% $NaHCO_3$

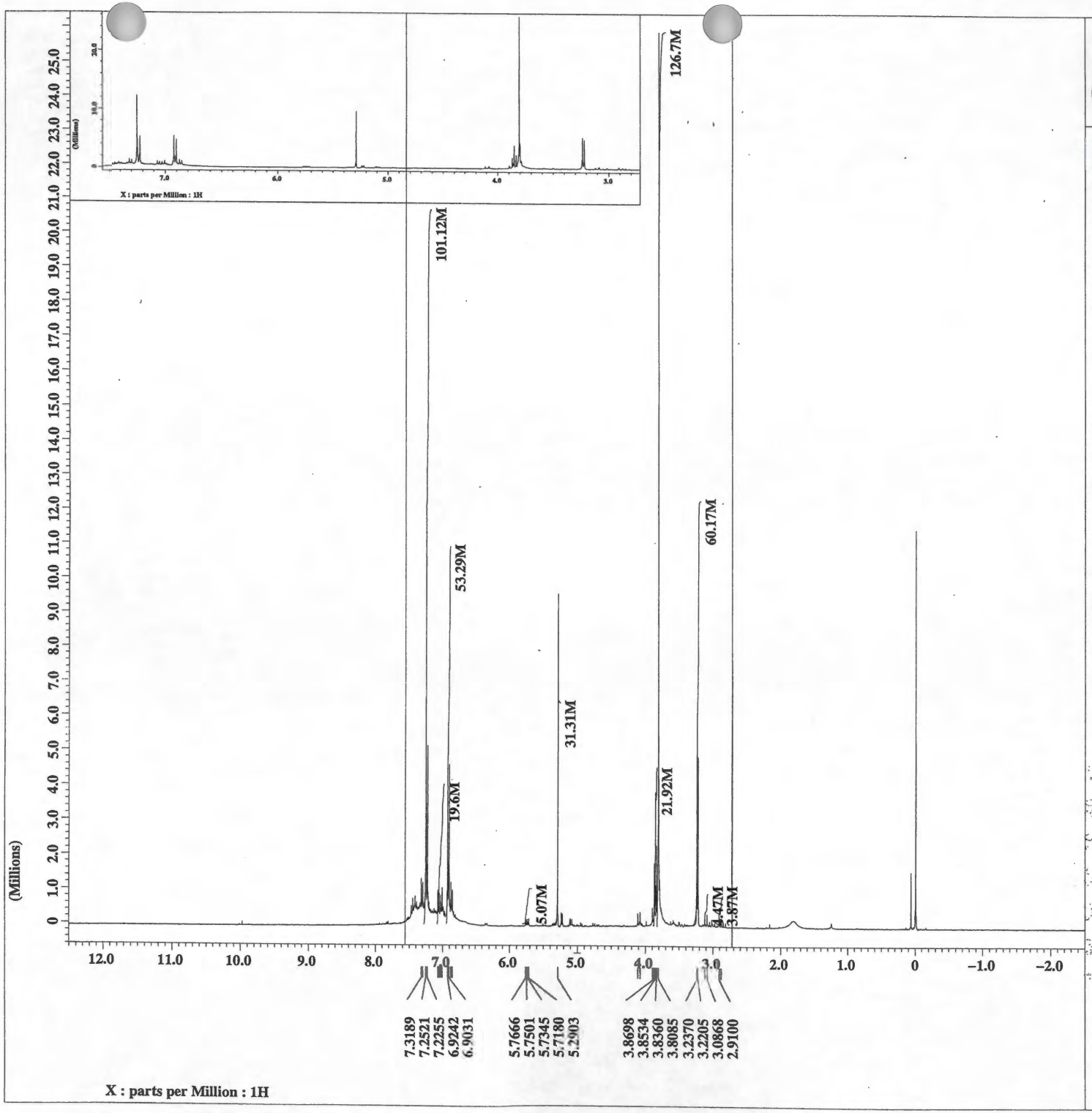
J. ^1H NMR 2-[1-(4-chlorophenyl)-2-nitro-ethyl]-2-(4-methoxybenzyl)malononitrile; 2% Na_2CO_3



A (4-methoxybenzylmalononitrile)



B (4-chloro-β-nitrostyrene)



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Revision_time	= 10-MAY-2016 17:09:09
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X_domain	= 1H
X_freq	= 399.78219838[MHz]
X_offset	= 5[ppm]
X_points	= 16384
X_prescans	= 0
X_resolution	= 0.36613771[Hz]
X_sweep	= 5.99880024[kHz]
Clipped	= FALSE
Mod_return	= 1
Scans	= 8
Total_scans	= 8
X_90_width	= 9.1[us]
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Initial_wait	= 1[s]
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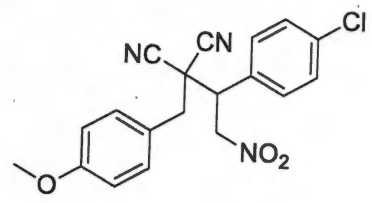
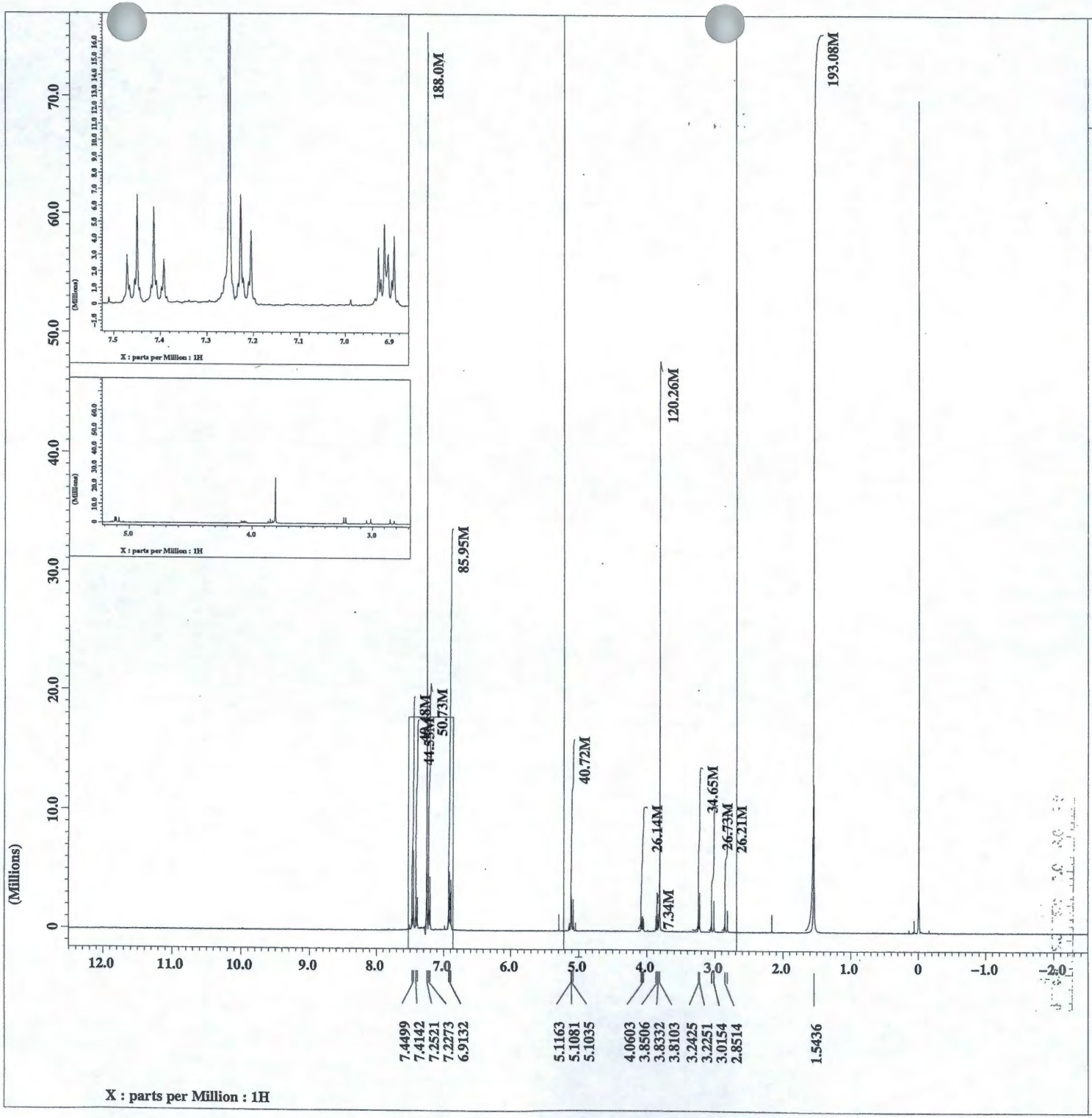


C (100, K2CO3)



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Field_strength	= 9.389766[T] (400[MHz]
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X_domain	= 1H
X_freq	= 399.78219838[MHz]
X_offset	= 5[ppm]
X_points	= 16384
X_prescans	= 0
X_resolution	= 0.36613771[Hz]
X_sweep	= 5.99880024[kHz]
Clipped	= FALSE
Mod_return	= 1
Scans	= 8
Total_scans	= 8
X_90_width	= 9.1[us]
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Initial_wait	= 1[s]
Phase_preset	= 3[us]
Recvr_gain	= 24
Relaxation_delay	= 4[s]
Temp_get	= 21.9[dC]
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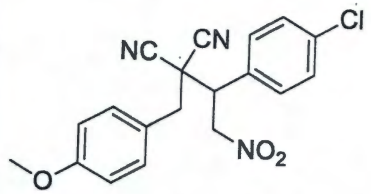
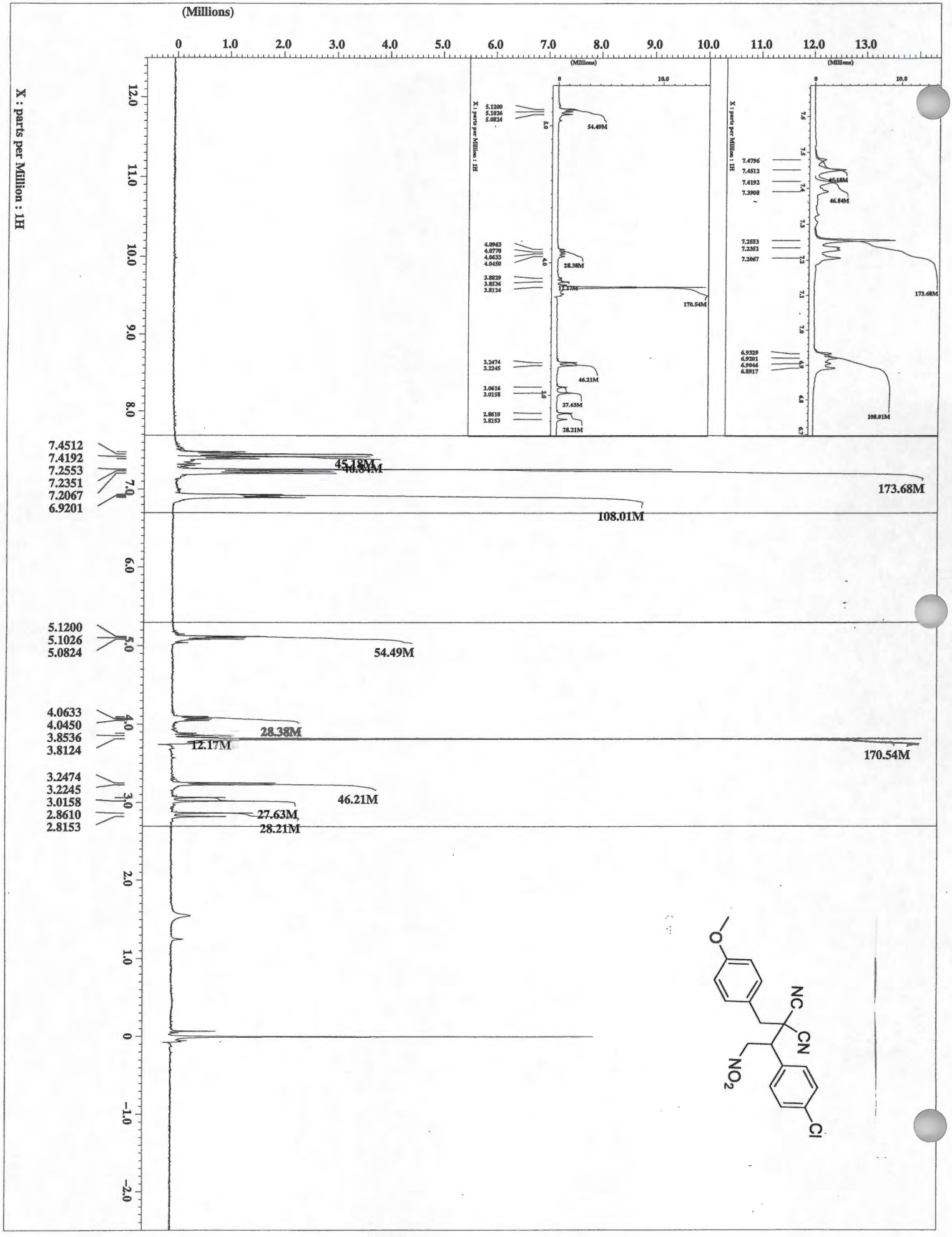


D (10% K2CO3)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X : parts per Million : 1H
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7.2553
7.2351
7.2067
6.9201
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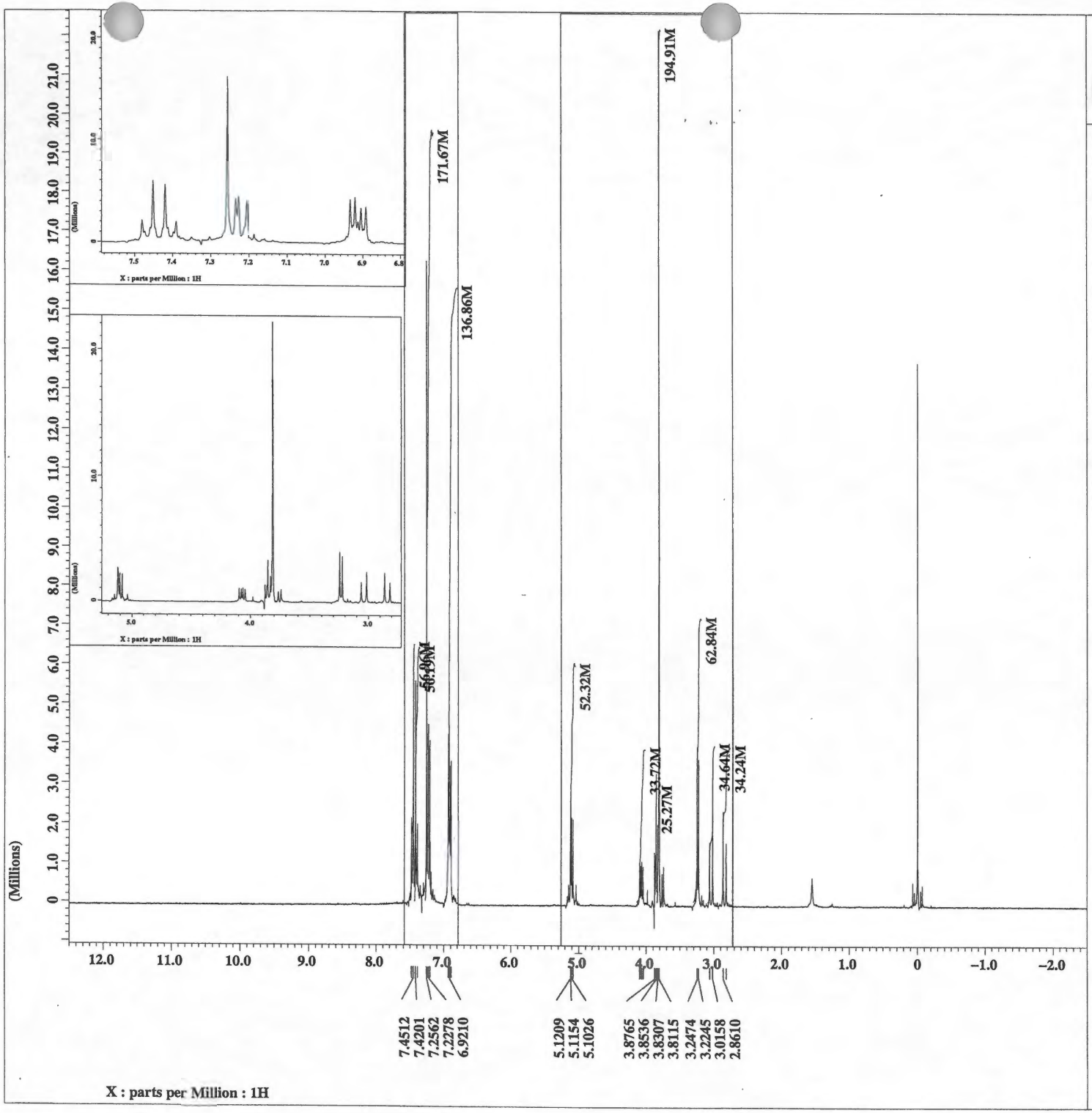
46.84M
173.68M
108.01M
5.1200
5.1026
5.0824
54.49M
4.0633
4.0450
3.8536
3.8124
28.38M
12.17M
170.54M
3.2474
3.2245
3.0158
2.8610
2.8153
46.21M
27.63M
28.21M
O
NC
CN
NO2
Cl

E (Z7. K2CO3)



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Revision_time	= 10-MAY-2016 17:49:28
Current_time	= 10-MAY-2016 17:50:31
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Data_format	= 1D COMPLEX
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X_points	= 16384
X_prescans	= 0
X_resolution	= 0.27518105[Hz]
X_sweep	= 4.50856628[kHz]
Clipped	= FALSE
Mod_return	= 1
Scans	= 8
Total_scans	= 8
X_90_width	= 12.4[us]
X_acq_time	= 3.6339712[s]
X_angle	= 45[deg]
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Initial_wait	= 1[s]
Phase_preset	= 3[us]
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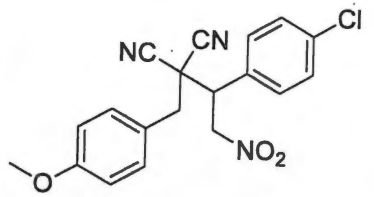
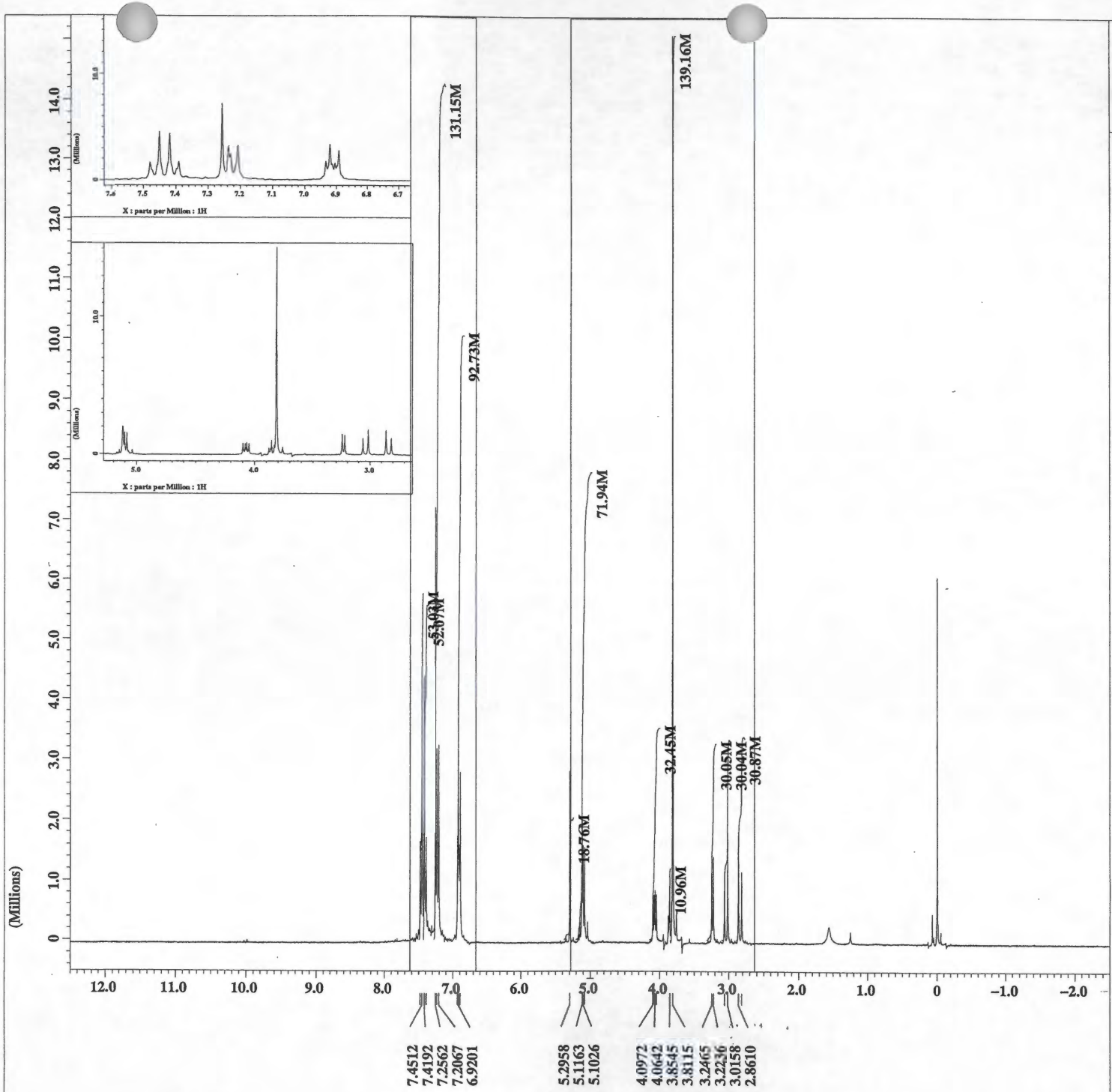


F (107. Na2CO3)



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X_offset	= 5[ppm]
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X_resolution	= 0.27518105[Hz]
X_sweep	= 4.50856628[kHz]
Clipped	= FALSE
Mod_return	= 1
Scans	= 8
Total_scans	= 8
X_90_width	= 12.4[us]
X_acq_time	= 3.6339712[s]
X_angle	= 45[deg]
X_pulse	= 6.2[us]
Initial_wait	= 1[s]
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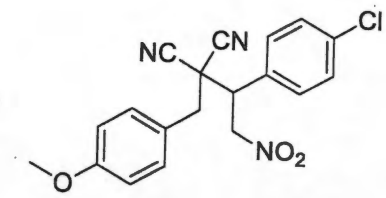
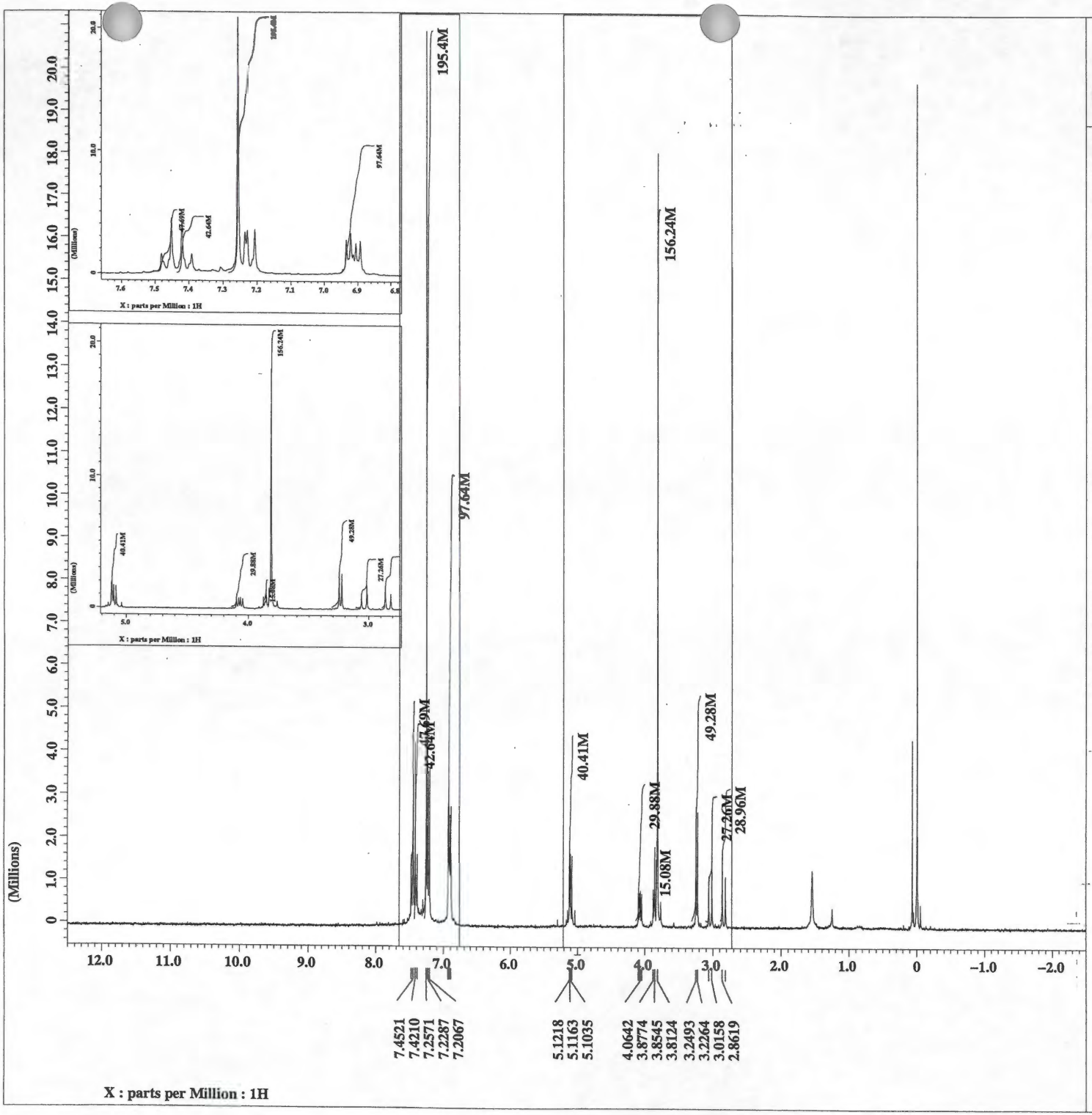


G (0.5h, K2CO3)



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X_offset	= 5[ppm]
X_points	= 16384
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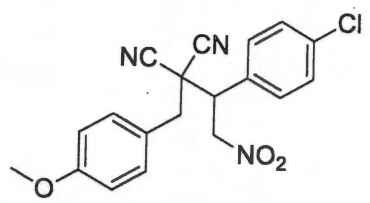
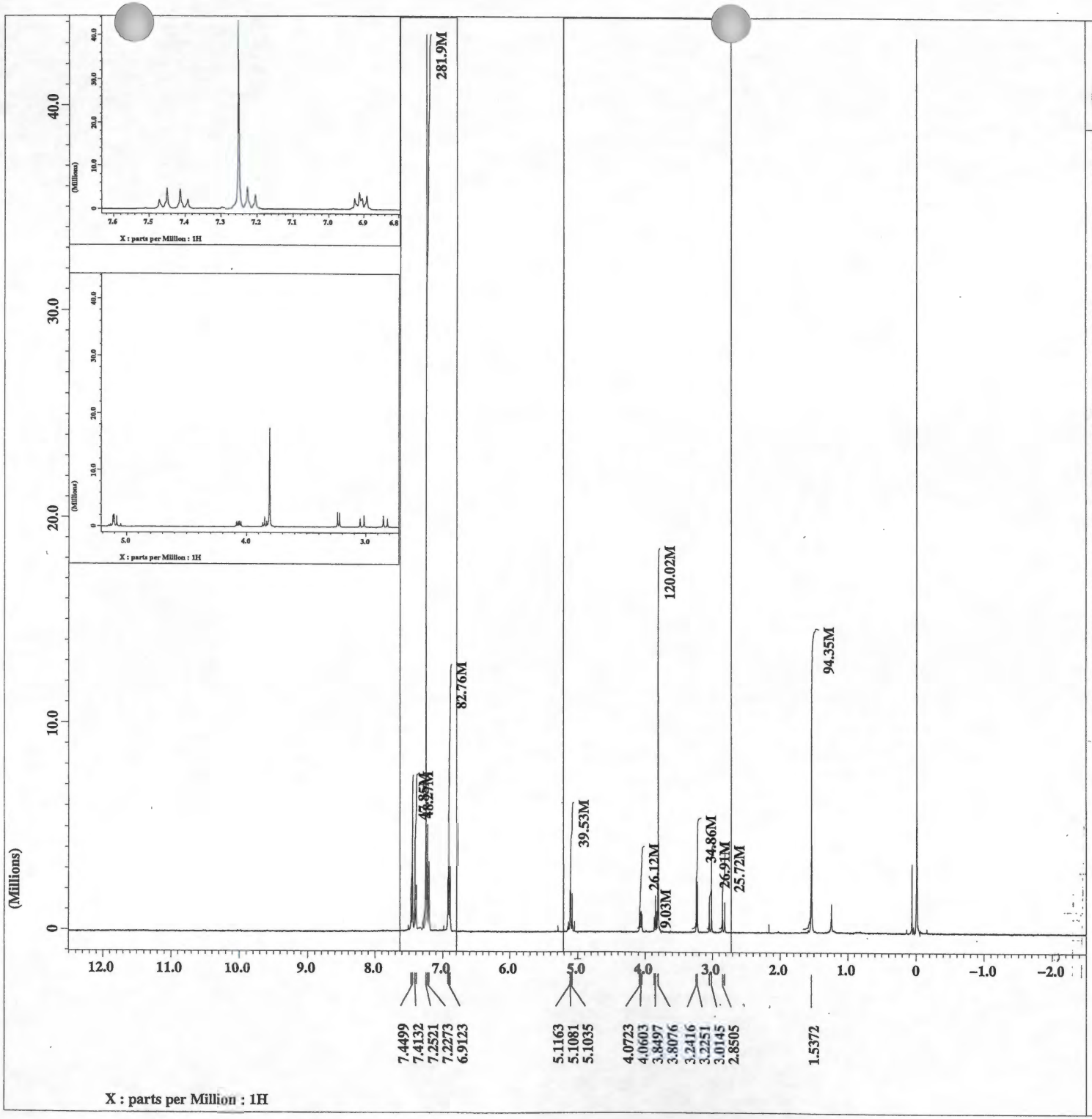
X_resolution	= 0.27518105[Hz]
X_sweep	= 4.50856628[kHz]
Clipped	= FALSE
Mod_return	= 1
Scans	= 8
Total_scans	= 8
X_90_width	= 12.4[us]
X_acq_time	= 3.6339712[s]
X_angle	= 45[deg]
X_pulse	= 6.2[us]
Initial_wait	= 1[s]
Phase_preset	= 3[us]
Recvr_gain	= 24
Relaxation_delay	= 4[s]
Temp_get	= 23[dC]
Unblank_time	= 2[us]



H (107. NaHCO3)



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Current_time	= 10-MAY-2016 18:03:20
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Spectrometer	= DELTA_NMR
Field_strength	= 9.389766[T] (400[MHz]
X_acq_duration	= 2.7312128[s]
X_domain	= 1H
X_freq	= 399.78219838[MHz]
X_offset	= 5[ppm]
X_points	= 16384
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X_resolution	= 0.36613771[Hz]
X_sweep	= 5.99880024[kHz]
Clipped	= FALSE
Mod_return	= 1
Scans	= 8
Total_scans	= 8
X_90_width	= 9.1[us]
X_acq_time	= 2.7312128[s]
X_angle	= 45[deg]
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Relaxation_delay	= 4[s]
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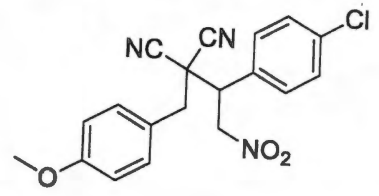
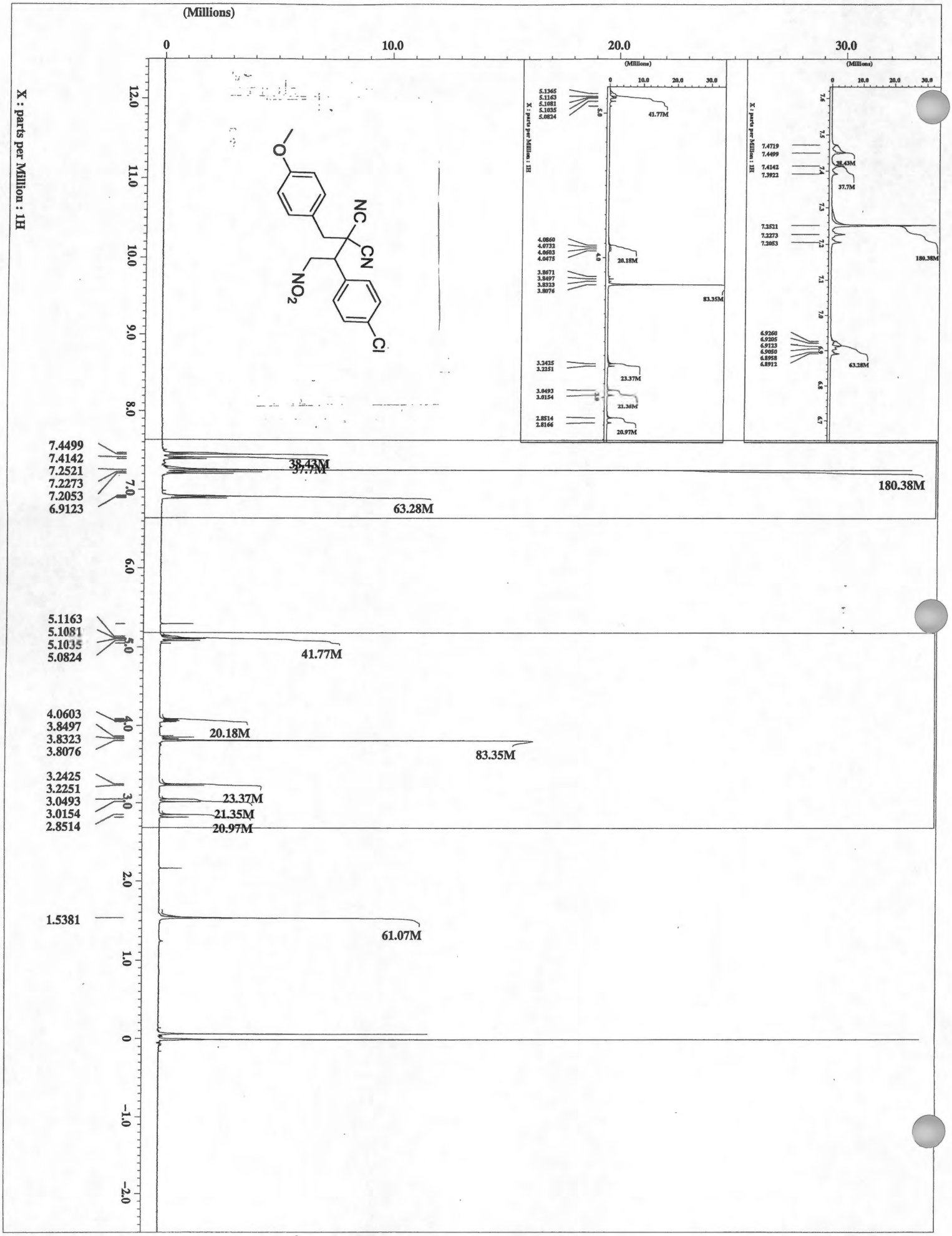


I (27. NaHCO3)


(Millions)
X : parts per Million : 1H
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7.4142
7.2521
7.2273
7.2053
6.9123
5.1163
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5.0824
4.0603
3.8497
3.8323
3.8076
3.2425
3.2251
3.0493
3.0154
2.8514
1.5381
38.43M
37.7M
180.38M
63.28M
41.77M
20.18M
83.35M
23.37M
21.35M
20.97M
61.07M
NC
CN
NO2
Cl
O

(27. NaC_{03})